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Journal Name:	Annual Research & Review in Biology
Manuscript Number:	2013_ARRB_7229
Title of the Manuscript:	Initial insight to effect of exercise on maximum pressure in the aortic root using 2D fluid-structure interaction model
Type of the Article	Original Research Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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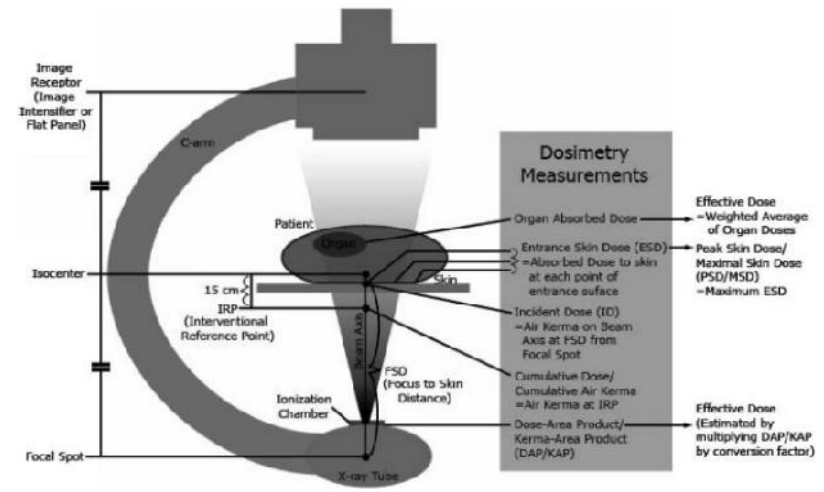


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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	<ol style="list-style-type: none"> 1. The methods are not clearly described at all. I do not understand what are the in- and outputs of the computation. 2. Many empirical relations are used, whose physiological relevance is never discussed. In particular, the authors state that there exists a nearly perfect ($r^2 = 0.995$) relation between cardiac output and heart rate, which neglects the influence of preload, afterload and contractility. 3. The authors manipulate these relations and come up with other ones, for which they get another r^2. These computations are not clear to me. 4. The authors refer to a paper published by Christie et al. (1987) for two empirical correlations, but I have not been able to find these correlations in said paper. 5. The authors state that the thermodilution technique implies radiations, which is something I am not aware of. This requires 	<p>The responses are highlighted in yellow.</p> <ol style="list-style-type: none"> 1. Inputs are cardiac outputs measured by echo-Doppler, as non-invasive and conventional method. Next step is modification of that based on reported between invasive and non-invasive results performed by Christie et al (1978). After that, we are going to estimate maximum pressure of left ventricle based on acquired relationship gained by Bahraseman et al [27] as the outputs. Please see newly added workflow diagram as figure 1. 2. The gained correlation factor ($r^2=0.995$) was the results of ref [27] which was done for healthy subject at different heart rates and was recently published. There was no any pre or after load. The heart rate increase was done by bicycle and hemodynamics were recorded at different heart rates. Such good correlations was reported; most of which were results stemmed from comparison between numerical and echo-Doppler measurements. However, it should be noted that the aim of this study was to propose the initial method to measure MPLV non-invasively. Of course, some further investigation should be done to certify the method for clinical applications. Please see conclusion section of abstract. 3. The equations 3 and 4 were results of curve fitting through the points (related to those shown in figure 4 for VSP and CDP) in Matlab. The performed r^2 show the quality of curve fitting technique. In other words, the more the r^2 are closer to 1, the more the curve fitting equation covers the points exactly. 4. As performed in table 2 of their paper: $COD = 0.71 COT + 1.7$

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	<p>justification.</p> <ol style="list-style-type: none"> The language of the paper is quite poor. The fact that the model is two-dimensional should be mentioned before the discussion. The authors should specify the units they use, as the coefficients of their empirical correlations depend on these units. 	<p>COD = 0.97 COF – 2.1 Where CO units are in l/min Therefore, with changing the unit to ml/min and arranging the above equations for COT and COF, equations 6 & 7 were achieved.</p> <ol style="list-style-type: none"> To show how a patient is exposed, the below figure was provided: [Ref]: Einstein, Andrew J., et al. "<u><i>Radiation dose to patients from cardiac diagnostic imaging.</i></u>" <i>Circulation</i> 116.11 (2007): 1290-1305.  <p>The diagram illustrates a patient undergoing cardiac diagnostic imaging. It shows the X-ray tube, image receptor, and various dosimetry measurements. The patient is positioned at the isocenter, with the X-ray tube and image receptor at a distance of 15 cm. The diagram also shows the entrance skin dose (ESD), incident dose (ID), and cumulative dose/area product (DAP/KAP). The diagram is labeled with various terms: Image Receptor (Image Intensifier or Flat Panel), Collimator, Patient, Isocenter, 15 cm, IRP (Interventional Reference Point), Ionization Chamber, Focal Spot, X-ray Tube, Skin, Organ, Entrance Skin Dose (ESD), Incident Dose (ID), Cumulative Dose/ Area Product (DAP/KAP), and Dosimetry Measurements. The Dosimetry Measurements section includes: Organ Absorbed Dose, Entrance Skin Dose (ESD), Incident Dose (ID), Cumulative Dose/ Area Product (DAP/KAP), and Effective Dose. The Effective Dose is defined as the weighted average of organ doses, peak skin dose/ maximal skin dose (PSD/MSD), and maximum ESD. The Effective Dose is also estimated by multiplying DAP/KAP by a conversion factor.</p> <ol style="list-style-type: none"> The paper was amended grammatically. All minor and optional/general comments including correcting grammatical mistakes were corrected and highlighted in yellow. This was noted at the first sentence of “2.1 Overview” section and referenced to our previous paper. This was not described in detail at this paper due to avoiding any overlap between and the former and latter papers.
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		8. They were applied in section 2.3 and anywhere that was necessary.
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<u>Minor</u> REVISION comments	<ol style="list-style-type: none"> 1) Line 135: Matlab should be referred to as "MATLAB (Version, MathWorks, Natick, MA)" and not included in the references. 2) There is a confusion between "CDP" and "ADP" in Figure 4 and its legend. 3) « mmHg/heart rate" is not a valid unit. It should be "mmHg*s" or "mmHg*min", according to how the heart rate is expressed. 4) Lines 46-47: "heart" is repeated. 5) Line 106: Please explain what a valsalva is. 	<ol style="list-style-type: none"> 1) Related ref ([40]) was added. 2) The figure 5 was amended and CDP was replaced by ADP 3) Unit of mmHg/heart rate was changed to mmHg*min 4) One of them was omitted 5) Each aortic sinus can also be referred to as the sinus of Valsalva. Please see line 111
<u>Optional/General</u> comments	<ol style="list-style-type: none"> 1) The abbreviation MPLV is introduced twice. 2) Line 40: the verb "progressed" seems to be misused. 3) The paragraph running from line 141 to line 149 should be made much shorter for better understanding. 4) I did not understand the meaning of the two sentences in lines 185 to 187. 5) There is something wrong with the prepositions in the sentence: "The FSI simulation can be used to determine a numerical relationship between the cardiac output to aortic diastolic and left ventricular pressures." 6) Line 60: "fluid-structure interaction" should be replaced by "FSI" since you introduced the 	<ol style="list-style-type: none"> 1) The second definition was omitted 2) That was changed to introduced 3) With using related abbreviations, the paragraph was shortened. Please also see abbreviation section line 349. 4) The mean slop refers to e.g. $(VSP_{max}-VSP_{min})/(hr_{max}-hr_{min})$. the lines were edited an amended. Please see line 204. 5) The sentence was corrected 6) The amendment was applied. 7) The amendment was applied. 8) That was corrected. 9) That was corrected. 10) That was amended. 11) That was corrected 12) That was corrected. 13) That was done 14) That was corrected 15) That was corrected 16) That was corrected 17) That was corrected 18) That was corrected 19) That was corrected



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	<p>abbreviation</p> <p>7) Line 63: "hemodynamics" instead of "hemodynamic"</p> <p>8) Line 72: no capital letter at "cardiac".</p> <p>9) Line 84: "to calculate" or "to derive" but not both.</p> <p>10) Line 445: the legend of Figure 3 is not explicit.</p> <p>11) Line 122: no capital letter at "left"</p> <p>12) Line 123: no capital letter at "aortic"</p> <p>13) Line 125 and 126: For clarity, I would suggest using an exponent rather than the "E" notation.</p> <p>14) Line 154: no capital letter at "thermodilution"</p> <p>15) Line 156: no capital letter at "thermodilution"</p> <p>16) Line 169: "in order to estimate the" instead of "in order to estimation of"</p> <p>17) Line 179: no capital letter at "thermodilution"</p> <p>18) Line 191: no capital letter at "one"</p> <p>19) Line 198: "lets" instead of "let"</p> <p>20) Line 203: no capital letter at "thermodilution"</p> <p>21) Line 229: no capital letter at "thermodilution"</p> <p>22) Capitalize the first letter for "table", "equation" and "figure".</p>	<p>20) That was corrected</p> <p>21) That was corrected</p> <p>22) That was corrected</p>
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